AMENDMENTS TO THE SPECIFICATION:

Please replace the title of the application as listed on page 1, line 1 with the following new title:

A1

--~~NOVEL COMPOSITIONS AND~~ METHODS OF SCREENING FOR B CELL ACTIVITY MODULATORS--

Please delete the heading on page 1, lines 3-4 as follows:

~~STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT~~

Please add the following new paragraph as the first sentence after the title on page 1:

A2

--CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/171,796, filed December 22, 1999, which is incorporated herein by reference.--

Please replace the paragraph beginning at page 5, line 30 with the following rewritten paragraph:

--~~FIG. 1.~~**FIGS. 1A - 1D**: Gene expression changes in B lymphocytes responding to foreign antigen. **FIG. 1A.** Genes with increased mRNA levels after 1 hr stimulation. 37 genes that showed significantly ($p<0.00018$) increased expression (see methods) and showed a median fold change of >1.75 were sorted by putative function. (CD72 is also shown but only increased 1.5 fold. BL34 is represented twice on the arrays, both sets of data are shown.) Each line represents one experiment. The left end of the line shows hybridization intensity in resting B cells mock stimulated in medium alone for one hour, the right end of the line shows intensity

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in B cells stimulated for one hour through the antigen receptor. Of the seven experiments shown, 3 experiments were with Ig^{HEL} transgenic B cells stimulated with medium alone or with HEL, and 4 experiments were with non-transgenic B cells stimulated with medium alone or with anti-mu. Analysis of variance showed that the basal profiles and responses to stimulation for Ig^{HEL} and non-transgenic B cells were essentially identical and the results have been presented together for clarity. Spiking known concentrations of bacterial transcripts allows an approximate calibration of 5 intensity units/copy/cell assuming 300, 000 transcripts per cell. **FIG. 1B.** Genes with decreased mRNA levels after 1 hr stimulation. Hybridization intensities are represented as for FIG. 1A. (GILZ is represented twice on the arrays, both sets of data are shown.). **FIG. 1C.** 1 and 6 hr timepoints of transcripts increased at 1 hr. Results are from 2 experiments showing HEL stimulation of Ig^{HEL} transgenic B cells. Each experiment is represented by a line. The left end of the line is the intensity of the transcript in B cells mock stimulated for 1 hr, the middle of the line is the intensity after 1 hr stimulation with HEL, the end of the line is the intensity after 6 hr stimulation with HEL. Genes are shown in order of exaggerated, sustained and transient increases relative to mock and 1 hr stimulated samples. **FIG. 1D.** 1 and 6 hr timepoints of transcripts decreased at 1 hr. Results are from 2 experiments with HEL stimulation of Ig transgenic B cells and are represented as in FIG. 1C.--

Please replace the paragraph beginning on page 6, line 23 with the following rewritten paragraph:

--~~FIG. 2~~**FIGS. 2A and 2B.** Gene expression changes in B lymphocytes responding to self antigen. **FIG. 2A.** Genes upregulated in tolerant cells compared to naïve cells. The left end of each line represents hybridization level in naïve Ig^{HEL} cells, the right end of the line represents hybridization level in tolerant sHEL/ Ig^{HEL} cells. Data points that are joined are from separate cell populations from genetically distinct animals - each line represents samples prepared in parallel on the same day. Five sets of data were derived from negatively depleted B cell preparations and two sets from FACS-sorted cells. One set of preparations included two tolerant cell samples and one naïve cell sample. This set is represented as 2 lines joining the

naïve cell hybridization intensity to each of the tolerant cell intensities. **FIG. 2B.** Genes downregulated in tolerant cells compared to naïve cells. Data is represented as in FIG. 2A.--

Please replace the paragraph beginning on page 7, line 1 with the following rewritten paragraph:

--~~**FIG. 3**~~**FIGS. 3A-3D.** Gene expression changes in B lymphocytes responding to foreign antigen in the presence of FK506 or PD98059. **FIG. 3A.** FK506 sensitivity of the 1 hr upregulated genes defined in FIG. 1. B cells were stimulated in the presence or absence of FK506, or were mock stimulated. Data are shown from 5 experiments and genes are shown in increasing order of median FK506 sensitivity. Each line represents one experiment. The left end of the line is hybridization intensity in resting B cells, the middle of the line is intensity in B cells stimulated for one hour through the antigen receptor and the right end of the line is intensity in B cells stimulated for one hour in the presence of FK506. Of the five experiments shown, 3 experiments were with IgHEL transgenic B cells stimulated with medium, HEL or HEL/FK506, and 2 experiments were with non-transgenic B cells stimulated with medium, anti-mu or anti-mu/FK506. **FIG. 3B.** FK506 sensitivity of the 1 hr down-regulated genes. Data is represented as for FIG. 3A. **FIG. 3C.** Correlation between sensitivity to FK506 and sensitivity to EGTA for antigen-induced transcripts. For the 37 induced genes defined in FIG. 1A, the relative induction in the presence of EGTA was calculated as average (antigen/EGTA-mock)/(antigen-mock), in two experiments with IgHEL transgenic cells stimulated with HEL. For the same transcripts, relative induction in the presence of FK506 was calculated as median of (antigen/FK506-mock)/(antigen-mock) over 5 experiments. **FIG. 3D.** Upper two panels: upregulation of Egr-1 by anti-mu stimulation of non-transgenic B cells is inhibited by PD98059 with an IC50 of ~5 μM. Regulation of other 1 hour response genes is less sensitive to PD98059. Lower panel: 3 transcripts upregulated by both foreign and self antigen are sensitive to PD98059. Left most four columns for each gene represent data from non-transgenic B cells stimulated with anti-mu, right most 3 columns represent data from Ig^{HEL} transgenic B cells stimulated with HEL.--

Please replace the paragraph beginning on page 7, line 25 with the following rewritten paragraph:

--~~FIG. 4A~~**FIGS. 4A and 4B**. **FIG. 4A.** Summary table of biochemical pathways in tolerant cells and naïve cells exposed to foreign antigen in the presence or absence of FK506 and PD98059. **FIG.4B.** Potential mechanisms of tolerance, immunity and immunosuppression suggested by the gene expression analysis. Font size reflects mRNA or protein expression level relative to mock stimulated cells (immunosuppression and activation panels) or naïve cells (tolerance panel). Tolerant cells have decreased surface IgM (sIgM) but increased IgD (mRNA and protein): sIg engagement by self-antigen causes decreased tyrosine phosphorylation relative to activated cells. Proximal signaling from sIg can be modulated in activated and tolerant cells by recruitment of SHP1 by increased CD72. Activation of naïve cells causes a robust calcium flux that triggers NFkB, JNK and NFAT. All these pathways are blocked by FK506 through inhibition of calcineurin: calmodulin action can be regulated in naïve and immunosuppressed cells by neurogranin and in tolerant cells by neurogranin and pcp-4. Egr family transcription is predicted to be different under the 3 conditions: in activated cells both Egr-1 and Egr-2 are upregulated preceding upregulation of NAB2; in immunosuppressed cells, only Egr-1 is upregulated; and in tolerant cells Egr-1 and Egr-2 are only weakly upregulated and can have different effects on transcription in the presence of increased NAB2. The balance between mitosis and apoptosis is likely to be in part determined by upregulation of the proto-oncogenes c-myc and LSIRF and the anti-apoptotic gene A1 in activated cells. These changes are blocked by tolerance and partially blocked by FK506. Downregulation of LKLF, which is sufficient to cause T cell activation, is partially inhibited by FK506 and is blocked in tolerance. Upregulation of surface activation markers CD69 and B7.2 is uninhibited by FK506 but is blocked in tolerance. The level of B7.2 on B cells is critical in interaction with antigen specific T cells.--

Please replace the paragraph beginning on page 55, line 10 with the following rewritten paragraph:

--Nonviral vectors encoding products useful in gene therapy can be introduced into an animal by means such as lipofection, biolistics, virosomes, liposomes, immunoliposomes, polycation: nucleic acid conjugates, naked DNA, artificial virions, agent-enhanced uptake of DNA, ex vivo transduction. Lipofection is described in *e.g.*, U.S. Patent Nos. 5,049,386, 4,946,787; and 4,897,355) and lipofection reagents are sold commercially (*e.g.*, ~~Transfectam™ and Lipofectin™~~ TRANSFECTAM™ AND LIPFECTIN™). Cationic and neutral lipids that are suitable for efficient receptor-recognition lipofection of polynucleotides include those of Felgner, WO 91/17424, WO 91/16024.--